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(54) Title: COMPOSITION FOR TREATMENT AND PREVENTION OF OBESITY AND ADULT DISEASE

(57) Abstract: The present invention relates to a composition comprising extracts of C *oix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* as an active ingredient for the treatment and prevention of obesity and adult disease. The present invention, the composition comprising the above described extracts show decreasing effect on the body weight, blood pressure and cholesterol, therefore, it can be used as the therapeutics or health food for treating and preventing obesity and adult diseases.

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Description

COMPOSITION FOR TREATMENT AND PREVENTION OF OBESITY AND ADULT DISEASE

Technical Field

[1] The present invention relates to the composition comprising extracts of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* for treating and preventing obesity and adult diseases.

Background Art

[2] Obesity is the most dangerous factor among adult chronic disease and induces to various diseases such as diabetes mellitus, hypertension, str ok e and cancer (National Heart, Lung and Blood Institute, 1998). Recently, the incidence rate of obesity has been increased to the extent that about 25% Korean adult were suffered from over-weight and obesity problems (Ministry of Health and Welfare; KHIDI, *'A deep analysis of the citizen healthy nutrition in 1998(I)'*, 2001). Obesity works as a risk factor in respect of health as well as the simple problems in respect of beauty. Therefore, BMI (Body Mass Index) value has been used as a judging standard of obesity and over-weight. There has been reported that the BMI values over 25 and 30 indicate over-weight and obesity respectively in case of western people and the BMI value above 23 indicates over-weight and the precaution of adult disease. (Korean Society for the Study of Obesity, The diagnosis and treatment of obesity, Asia & Pacific Region guideline, 2000).

[3] There have been several methods to treat obesity, for example, diet therapy or exercise therapy, however, those methods often result in failure because of genetic factor such as personal differences in respect to appetite, favor to high-fat food and metabolism of fat formation. Accordingly, there have been eagerly needed to develop new therapy to promote reducing body weight or new medicine other than classical approach methods.

[4] *Coix lachrymajobi* belonged to *Poaceae*, has been cultivated in Korea , and used as a food including tea, health food etc and a Chinese medicine to prevent or treat in-flammation or pain etc. It has been reported to contain 16.2% protein, 465% fat, 50% starch, 2% ash and a small quantity of vitamin (Chung B. S. and Shin M. K.; HyangyakDaesacheon, Youngrimsa. pp212, 1998).

[5] *Castanea crenata* belonged to *Fagaceae*, has been cultivated in Korea , and used as a favorable food and a Chinese medicine in the form of an un-husked seed to prevent

gastric disease etc. It has been reported to contain 5.7% protein, 2.0% fat, 1.3% inorganic ingredient, vitamins and several enzymes (Chung B. S. and Shin M. K.; HyangyakDaesacheon, Youngrimsa. pp212, 1998).

[6] *Cervus elaphus* , a cornu of deer, has been used as a health food and a Chinese medicine to prevent anemia disease etc. It has been reported to contain abundant amount of calcium.

[7] *Schizandra chinensis* belonged to *Magnoliaceae*, has been cultivated in Korea , and used as a food including tea, health food etc and a Chinese medicine as in the form of a fructus to prevent or treat hypertension and cough etc. It has been reported to contain 12% citral, 10% malic acid and abundant amount of essential oil such as sesqui-carene, bisabolene and chamigrene (Chung B. S. and Shin M. K.; HyangyakDaesacheon, Youngrimsa. pp472, 1998).

[8] *Nelumbo nucifera* belonged to *Nymphaeaceae*, has been cultivated in Korea , and used as a food including tea, health food etc and a Chinese medicine in the form of an un-husked seed to prevent or treat psychological disease such as insomnia, heart palpitation or diarrhea etc. It has been reported to contain raffinose, methylcorypalline, lotusine chloride, liensinine, 16.6% protein, 2% fat acid and 0.089% calcium ion etc (Chung B. S. and Shin M. K.; HyangyakDaesacheon, Youngrimsa. pp514, 1998).

[9] Redux™ (Knolls Corp. Germany) recently approved for market reduces body weight by acting on brain and inhibiting appetite and Xenical™ (ingredient: orlistat, Roche Pharm. Co. Swiss) reduces the absorption of ingested fat up to 30%. However, it has been reported that those drugs have several disadvantages such as the occurrence of breast cancer, long term toxicity etc. (http://www.yahoo.com/Health , Reuters, Jun. 1997).

[10] Korea Patent Publication No. 2002-0092640 (Dec. 12, 2002) discloses α-lipoic acid as an obesity treating agent and Korea Patent Publication No. 2003-0011474 (Feb. 11, 2003) discloses a polyacetylene compound isolated from ginseng useful to treat obesity by way of inhibiting the uptake of cholesterol in human body.

[11] Korea Patent Publication No. 2002-0069506 (Sep. 4, 2002) discloses a tea extract useful to treat obesity by way of inhibiting the transformation of starch to disaccharide, which reduces the uptake of calorie.

[12] However, there has been not reported or disclosed about therapeutic effect for obesity disease of *Coix lachrymajobi, Castanea crenata*, *Cervus elaphus*, *Schizandra chinensis* and *Nelumbo nucifera* in any of above cited literatures as incorporated herein as references.

[13] To investigate an effect of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* on obesity and adult disease, and to confirm whether the crude drug extract shows inhibiting effect on obesity or not, the inventors of the present invention have intensively carried out animal model *in vivo* experiments and clinical test cell line culture and finally completed present invention by confirming that the extract reduces the weight of fatty organ, the concentration of glucose and triglyceride in blood plasma in rat and body weight of men .

Disclosure

[14] The present invention provides a pharmaceutical composition comprising a crude drug extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis*and *Nelumbo nucifera* as the active ingredients to treat and prevent obesity disease and pharmaceutically acceptable carrier or adjuvant.

[15] The present invention also provides a use of above described extracts for the preparation of pharmaceutical composition to treat and prevent obesity disease in human or mammal.

[16] The present invention also provides a method of treating or preventing obesity in a mammal comprising administering to said mammal an effective amount of above described crude drug extract, together with a pharmaceutically acceptable carrier or adjuvant.

[17] The present invention also provides a health care food or food additives comprising above described extract, together with a sitologically acceptable additive for the prevention and improvement of obesity disease.

[18] Accordingly, it is an object of the present invention to provide a pharmaceutical composition comprising the crude extracts of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* as the active ingredients for the treatment and prevention of obesity disease and pharmaceutically acceptable carrier or adjuvant.

[19] Above described crude extracts comprises the extract prepared by extracting plant material with water, lower alcohols such as methanol, ethanol, preferably water.

[20] Preferable composition of the present invention may comprises the extract of crude drug consisting of 30 ~ 45% *Coix lachrymajobi,* 30 ~ 45% *Castanea crenata,* 1 ~ 15% *Cervus elaphus,* 2 ~ 10% *Schizandra chinensis* and 1 ~ 6% *Nelumbo nucifera* based on the total weight of the composition.

[21] Also, above described composition of the present invention may further comprise the extract of additional Chinese herbal selected from the group consisting of

Dioscorea batatas, Platycodon grandiflorum, Liriope platyphylla, Morus alba, Raphanus sativus, Pyrus ussuriensis, Prunus mune, Phyllostachys bambusoides and *Angelica keiskei.*

[22] It is an object of the present invention to provide a use of aforementioned crude drug extract for the preparation of therapeutic agent for the treatment and prevention of obesity disease in human or mammal.

[23] It is another object of the present invention to provide a health care food or food additives comprising above described extract, together with a sitologically acceptable additive for the prevention and improvement of obesity and adult disease.

[24] The pharmaceutical composition of the present invention can contain about 0.01 ~ 50 % by weight of above described extract based on the total weight of the composition.

[25] The health care food of the present invention comprises above described extract as 0.01 to 80 %, preferably 10 to 50 % by weight based on the total weight of the composition.

[26] Above described health care food can be contained in health food, health beverage etc, and may be used as powder, granule, tablet, chewing tablet, capsule, beverage etc.

[27] Above described term 'adult disease' herein indicates various diseases in men such as diabetes mellitus, hypertension, stroke and cancer.

[28] The inventive extracts isolated from *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* may be prepared in accordance with the following preferred embodiment.

[29] Hereinafter, the present invention is described in detail.

[30] The inventive extracts of the present invention can be prepared in detail by following procedures,

[31] The inventive crude drug extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* can be prepared by following procedure; for example, *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* are dried, cut, crushed and mixed with 5 to 15-fold, preferably, approximately 5 to 10 fold volume of distilled water, lower alcohols such as methanol, ethanol, butanol and the like, or the mixtures thereof, preferably distilled water; the solution is treated with hot water at the temperature ranging from 80 to 100 ° C, preferably 100 ° C, for the period ranging from 1 to 30 minutes with extraction method by the extraction with hot water with 1 to 5 times, preferably 2 to 5 times to obtain dried crude extract powder of *Coix lachrymajobi,*

Castanea crenata, Cervus elaphus, Schizandra chinensis and *Nelumbo nucifera* which can be soluble in water, lower alcohols, or the mixtures thereof.

[32] In accordance with another aspect of the present invention, there is provided a pharmaceutical composition comprising the crude drug extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* prepared by above described preparation method for the treatment and prevention of obesity and adult disease.

[33] It is another of the present invention to provide a method of treating or preventing obesity in a mammal comprising administering to said mammal an effective amount of above described crude drug extract prepared by above described preparation method, together with a pharmaceutically acceptable carrier or adjuvant.

[34] The inventive composition may additionally comprise conventional carrier, adjuvants or diluents in accordance with a using method well known in the art. It is preferable that said carrier is used as appropriate substance according to the usage and application method, but it is not limited. Appropriate diluents are listed in the written text of Remington's Pharmaceutical Science (Mack Publishing co., Easton PA).

[35] Hereinafter, the following formulation methods and excipients are merely exemplary and in no way limit the invention.

[36] The composition according to the present invention can be provided as a pharmaceutical composition containing pharmaceutically acceptable carriers, adjuvants or diluents, e.g., lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starches, acacia rubber, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, polyvinyl pyrrolidone, water, methylhydroxy benzoate, propylhydroxy benzoate, talc, magnesium stearate and mineral oil. The formulations may additionally include fillers, anti-agglutinating agents, lubricating agents, wetting agents, flavoring agents, emulsifiers, preservatives and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after their administration to a patient by employing any of the procedures well known in the art.

[37] For example, the compositions of the present invention can be dissolved in oils, propylene glycol or other solvents that are commonly used to produce an injection. Suitable examples of the carriers include physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc., but are not limited to them. For topical administration, the extract of the present invention can be formulated in the form of ointments and creams.

[38] Pharmaceutical formulations containing present composition may be prepared in any form, such as oral dosage form (powder, tablet, capsule, soft capsule, aqueous medicine, syrup, elixirs pill, powder, sachet, granule), or topical preparation (cream, ointment, lotion, gel, balm, patch, paste, spray solution, aerosol and the like), or injectable preparation (solution, suspension, emulsion).

[39] The composition of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

[40] The desirable dose of the inventive extract or composition varies depending on the condition and the weight of the subject, severity, drug form, route and period of administration, and may be chosen by those skilled in the art. However, in order to obtain desirable effects, it is generally recommended to administer at the amount ranging 10 g/kg, preferably, 1 to 3 g/kg by weight/day of the inventive extract of the present invention. The dose may be administered in single or divided into several times per day. In terms of composition, the amount of inventive extract should be present between 0.01 to 50% by weight, preferably 0.5 to 40% by weight based on the total weight of the composition.

[41] The pharmaceutical composition of present invention can be administered to a subject animal such as mammals (rat, mouse, domestic animals or human) *via* various routes. All modes of administration are contemplated, for example, administration can be made orally, rectally or by intravenous, intramuscular, subcutaneous, intracutaneous, intrathecal, epidural or intracerebroventricular injection.

[42] Also, the present invention provides a composition of the health food beverage for the prevention and improvement of obesity disease adding above described extract 0.01 to 80 % by weight, amino acids 0.001 to 5 % by weight, vitamins 0.001 to 2 % by weight, sugars 0.001 to 20 % by weight, organic acids 0.001 to 10 % by weight, sweetener and flavors of proper amount.

[43] Above described extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* can be added to food and beverage for the prevention and improvement of obesity and adult disease.

[44] To develop for health food, examples of addable food comprising above the composition of the present invention are various food, beverage, gum, vitamin complex, health improving food and the like, and can be used as power, granule, tablet, chewing tablet, capsule or beverage etc.

[45] Above described composition therein can be added to food, additive or beverage, wherein, the amount of above described extract in food or beverage may generally range from about 1 to 80w/w %, preferably 10 to 50 w/w % of total weight of food for the health food composition and 0.01 to 30 g, preferably 3 to 10 g on the ratio of 100 ml of the health beverage composition.

[46] Providing that the health beverage composition of present invention contains above described composition as an essential component in the indicated ratio, there is no particular limitation on the other liquid component, wherein the other component can be various deodorant or natural carbohydrate etc such as conventional beverage. Examples of aforementioned natural carbohydrate are monosaccharide such as glucose, fructose etc; disaccharide such as maltose, sucrose etc; conventional sugar such as dextrin, cyclodextrin; and sugar alcohol such as xylitol, and erythritol etc. As the other deodorant than aforementioned ones, natural deodorant such as taumatin, stevia extract such as levaudioside A, glycyrrhizin et al., and synthetic deodorant such as saccharin, aspartam et al., may be useful favorably. The amount of above described natural carbohydrate is generally ranges from about 1 to 20 g, preferably 5 to 12 g in the ratio of 100 ml of present beverage composition.

[47] The other components than aforementioned composition are various nutrients, a vitamin, a mineral or an electrolyte, synthetic flavoring agent, a coloring agent and improving agent in case of cheese chocolate et al., pectic acid and the salt thereof, alginic acid and the salt thereof, organic acid, protective colloidal adhesive, pH controlling agent, stabilizer, a preservative, glycerin, alcohol, carbonizing agent used in carbonate beverage et al. The other component than aforementioned ones may be fruit juice for preparing natural fruit juice, fruit juice beverage and vegetable beverage, wherein the component can be used independently or in combination. The ratio of the components is not so important but is generally range from about 0 to 20 w/w % per 100 w/w % present composition. Examples of addable food comprising afore-mentioned extract therein are various food, beverage, gum, vitamin complex, health improving food and the like.

[48] The inventive composition may additionally comprise one or more than one of organic acid, such as citric acid, fumaric acid, adipic acid, lactic acid, malic acid; phosphate, such as phosphate, sodium phosphate, potassium phosphate, acid pyrophosphate, polyphosphate; natural anti-oxidants, such as polyphenol, catechin, alpha-tocopherol, rosemary extract, vitamin C, green tea extract, licorice root extract, chitosan, tannic acid, phytic acid etc.

[49] The ratio of above described extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis*and *Nelumbo nucifera* may be 20 to 90 % in high concentrated liquid, power, or granule type.

[50] Similarly, the above described extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis*and *Nelumbo nucifera* can comprise additionally one or more than one of lactose, casein, dextrose, glucose, sucrose and sorbitol.

[51] The extract of the present invention have no toxicity and adverse effect therefore; they can be used with safe.

[52] It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

Description Of Drawings

[53] The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which;

[54] Fig. 1a and 1b show effect of KSH28 on epididymal adipose tissue of high fat diet-induced obese mice; Fig. 1a depicts H&E stained picture of epididymal adipose tissue (bar: 30 um, X100) and Fig. 1b shows mean cross-sectional area of fat cells in epididymal adipose tissue.

Best Mode

[55] It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

[56] The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

[57] **EXAMPLES**

[58] The following Examples and Experimental Examples are intended to further illustrate the present invention without limiting its scope.

[59] **Example 1. Preparation of powder**

[60] Each 2kg of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* waspurchased and washed with water. The external husk and blue seed in the fruit of *Nelumbo nucifera* were removed. All of above crude drugs were dried by natural air at room temperature for 3 or 4 days and dried again by hot wind for 1 week. The dried crude drugs were pulverized respectively with a

pulverizer to obtain five crude drug powders of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera.*

[61] **Example 2. Preparation of extract**

[62] The dried powder prepared in Example 1 was subject to extraction by following procedure. 5L of water was added to each 50g of the powder prepared in Example 1, heated at 100°C and cooled. The similar procedure to said extraction was repeated with 5 times to collect crude drug extract and dried to obtain 23.2g of *Coix lachrymajobi*, 20.1g of *Castanea crenata*, 19.8g of*Cervus elaphus*, 24g of *Schizandra chinensis* and 22g of *Nelumbo nucifera* respectively.

[63] **Example 3. Preparation of KSH28**

[64] Several Chinese herbs were added to above described extract prepared in Example 1 and 2, of which prescription was shown in Table 1 designated as KSH28 herein. The composition of KSH28 was created by the theological basis handed down from ancestor and old medicinal books.

[65] **Table 1**

Composition	Amount (g)	% Ratio
Coix lachrymajobi	45	37.19
Castanea crenata	45	37.19
Dioscorea batatas	1.6	1.32
Platycodon grandiflorum	1.8	1.49
Liriope platyphylla	1.5	1.24
Cervus elaphus	11.6	9.59
Morus alba	1.5	1.24
Raphanus sativus	0.8	0.66
Pyrus ussuriensis	0.8	0.66
Prunus mune	0.7	0.58
Schizandra chinensis	6.3	5.21
Phyllostachys bambusoides	0.3	0.25
Angelica Keiskei	0.6	0.50
Nelumbo nucifera	3.8	3.14
Sum	121	100

[66] **Example 4. Preparation of a natural food comprising the KSH28**

[67] As an exemplary market product of the present invention, The inventive natural food was prepared by adding KSH28 prepared in Example 3 to conventional following additives: grains such as brown rice, wheat, soybean, pea etc.; mushrooms such as oyster mushroom, shiitake fungus etc.; seaweeds such as dried laver, dried kelb etc.; vegetables such as carrot, Codonopsis root, lotus root etc.; dietary fibers such as glucomannan etc.; vitamins such as Vitamin B_1, B_2, B_6, D_3, and Vitamin C etc.; minerals such as calcium, Zn etc. The inventive natural food was packed by a volume of 30g for once dosage and the composition of those was shown in following Table 2.

[68] **Table 2**

Composition	Amount (g)	% Ratio
KSH28	12.04	40.10
Brown rice	9.00	30.00
Wheat	3.00	10.00
Soybean	2.27	7.58
Pea	0.60	2.00
Oyster mushroom	0.05	0.175
Shiitake fungus	0.06	0.20
Dried laver	0.09	0.30
Dried kelp	0.18	0.60
Carrot	0.05	0.18
Codonopsis root	0.03	0.10
Lotus root	0.15	0.50
Glucomannan	1.35	450
Vitamin B_1	0.0004	0.00125
Vitamin B_2	0.0005	0.00150
Vitamin B_6	0.0005	0.00175
Vitamin D_3	0.0001	0.00025
Vitamin C	0.0038	0.01250
Inositol	0.30	1.00

ZnO	0.0004	0.00125
L-organic calcium	0.60	2.00
Stevioside (50%)	0.15	0.50
Sum	30.00	100.00

[69] **Experimental Example 1. Animal model experiment**

[70] **1-1. Preparation of the Experimental Animal and Administration**

[71] 6 weeks year old C57BL/6 male mice (Daehan Biolink Co., Ltd., Korea) were acclimated for a week and used in obesity experiment for total 4 weeks. Experimental animals were classified with five groups, i.e., NC group (Control Diet), HNC group (High Fat Diet), KSH28-1 group, KSH28-2 group and AR25 group as a positive control. The component of control diet and high fat diet were shown in Table 3

[72] The administration dosage of each experimental groups was determined by the dosage of adult and the administration dosage of KSH28 was 12g/day based on traditional clinical dosage for 60kg of adult. KSH28 was orally administered once a day to KSH28-1 group and KSH28-2 group at a dosage of 0.2g/kg and 0.4g/kg respectively. As a positive control, 0.025g/kg (1.5g/60kg) of AR25 (Green Tea Ext. AR25®, Arkopharma , France , Exolise™) was administered to AR25 group once a day.

[73] **Table 3**

Component	Control Diet(%)	High Fat Diet(%)
Casein	20	20
Sucrose	10	10
Corn starch	39.75	31
Dyetrose	13.2	10
Lard (80%)	-	13.5
Soybean oil	7	5.5
Cellulose	5	5
Vitamin mix	1	1
Mineral mix	3.5	3.5
Choline bitartarate	0.25	0.2
L-Cystein	0.3	0.3

Butylhydroxy quinoline	0.0014	0.0014
Sum	100	100

[74] **1-2. Effect of the KSH28 on obesity and adult disease in animal experiment**

[75] Test drugs were orally administered at constant intervals once a day for 4 weeks and the change of weight was examined every week. Experimental animals had been fasted from 16 hours before experimental day and made to be general anesthesia with ether solvent to collect testing blood from heart. The blood plasma was separated from the blood by centrifugation at 3,500rpm and the content of serum glucose and neutral fat (Triglyceride, TG) in the blood were analyzed.

[76] The epididymal adipose tissue and retro-peritoneal adipose tissue were taken off from epididymis and their weight was measured. After rapidly freezing the fat tissue extracted from epididymal adipose tissue, the fat tissue was minced with freezing metronome (CM3050s, LEICA, German) to obtain a section at the thickness of 40 um, which was further stained with hematoxylin (Mayer's hematoxylin) dye. The cut area of stained sections was then examined under a light microscope (CK2, Olympus, Japan) and an image analysis program (Image and Micoroscope Technology Co., Korea) (*See* Fig. 1 and 2).

[77] The difference between each group was analyzed by one-way analysis of variance (ANOVA) and Duncan Test using a SPSS Package (ver. 9.0) and their statistical significance was accepted within alpha = 0.05, which was applied to calculate the average and a standard deviation of the present experiment.

[78] At the result of the experiment, the weight of mouse was significantly reduced by 6.4% in KSH28-1 group, 9.2% in KSH28-2 group respectively comparing with HNC group (*See* Table 4).

[79] The weight of retro-peritoneal adipose tissue in each group was reduced by 15.4% in KSH28-1 group, and 28.2% in KSH28-2 group, respectively, in a dose dependent manner. The weight of the epididymal adipose tissue was also reduced by 17.4% in KSH28-1 group, and 27.3% in KSH28-2 group. These results indicate that the decreased ratio of body fat is higher than that of the decreased ratio of body weight.

[80] Especially, the decreasing effect on the fat tissue in KSH28-2 was more potent than that of positive control group. The cell size of the epididymal adipose tissue in HNC group was more greatly increased than that in NC group (normal control group), which indicates the obesity was basically originated from the increased mean size of fat cell.

[81] Comparing with the area of fat cells under the cross sectional investigation in between KSH28-1 and KSH28-2 treatment groups, there was a reduction of the area by 60% in KSH28-1 and 80% in KSH28-2 respectively, in a dose dependent manner.

[82] **Table 4**

	NC (n=10)	HNC (n=15)	KSH28-1 (n=10)	KSH28-2 (n=10)	AR25 (n=10)
Body weight (g)	$26.5 \pm 0.6^{1)ab}$	28.2 ± 0.5^{b}	26.4 ± 1.1^{ab}	25.6 ± 0.6^{a}	26.5 ± 0.6^{ab}
Retro-peritoneal adipose tissue (g)	0.35 ± 0.02^{ab}	0.39 ± 0.02^{b}	0.33 ± 0.05^{ab}	0.28 ± 0.03^{a}	0.33 ± 0.04^{ab}
Epididymal adipose tissue (g)	1.17 ± 0.05^{ab}	1.32 ± 0.08^{b}	1.09 ± 0.16^{ab}	0.96 ± 0.08^{ab}	1.13 ± 0.14^{ab}

[83] $^{1)}$ Mean ± SE

[84] $^{a, b, c}$ Values marked by different alphabets were significantly different by ANOVA with post hoc. Duncan's test ($p<0.05$)

[85] NC : Group fed normal diet

[86] HNC : Group fed 30% high fat diet

[87] KSH28-1 : Group treated with 0.2g/Kg KSH28 with 30% high fat diet

[88] KSH28-2 : Group treated with 0.4g/Kg KSH28 with 30% high fat diet

[89] AR25 : Group treated with AR25, an anti-obesity drug

[90] **1-3. Effect of the KSH28 on the blood glucose and triglyceride**

[91] The amount of serum glucose and triglyceride in blood were significantly reduced by the treatment of the KSH28 in a dose dependent manner comparing with HNC group (*See* Table 5).

[92] **Table 5**

	NC (n=10)	HNC (n=15)	KSH28-1 (n=10)	KSH28-2 (n=10)	AR25 (n=10)
Glucose (mg/dL)	$200 \pm 8.1^{1)a}$	222 ± 11.3^{a}	172 ± 12.0^{b}	153 ± 9.2^{b}	174 ± 15.1^{b}
Triglyceride (mg/dL)	110 ± 47^{a}	118 ± 42^{a}	97 ± 49^{b}	88 ± 5.1^{bc}	73 ± 0.43^{c}

[93] [1)] Mean ± SE

[94] [a, b, c] Values marked by different alphabets were significantly different by ANOVA with post hoc. Duncan's test ($p<0.05$)

[95] NC : Group fed normal diet

[96] HNC : Group fed 30% high fat diet

[97] KSH28-1 : Group treated with 0.2g/kg KSH28 with 30% high fat diet

[98] KSH28-2 : Group treated with 0.4g/kg KSH28 with 30% high fat diet

[99] AR25 : Group treated with AR25, an anti-obesity drug

[100] **Experimental Example 2. Clinical Experiment**

[101] **2-1. The Research Subject and Method**

[102] The clinical experiment was accomplished by 40 numbers of people agreed to voluntary participation, and the characteristics of subjects were shown in Table 6.

[103] All the subjects had taken the inventive natural food comprising the KSH28 twice a day for 4 weeks and the examination of blood test and body composition analysis together with history taking were carried out at the starting time and after 4 weeks to all subjects. All subjects were allowed to take a food freely without diet-regulation and diet-management except fasting for 12 hours before clinical experiment.

[104] **Table 6**

Characteristics	Mean ± SE
Age	42.35 ± 2.25
Gender	M : F = 8 : 32
Body Weight	71.28 ± 1.97
BMI	27.40 ± 0.58

[105] **2-2. Effect of the KSH28 on the body sizes**

[106] The sizes of height, weight, waist and hip of all subjects were measured. The height and weight were measured with automatic height-weight measurement equipment (Jenix, Dongsintonsang) and the value of BMI i.e., the calculated index of height (cm)/weight $(kg)^2$, and the value of WHR (Waist-Hip Ratio) were calculated at the basis of the measured sizes of all subjects.

[107] At the result of the experiment, the values of weight, obesity index and BMI were significantly reduced. The size of waist was significantly reduced by 3.44cm on the average, however, the size of hip was not. Also, the index of WHR was significantly reduced. The weight was reduced by 1.91kg for 4 weeks, which indicates the weight

was reduced by 0.5kg per a week (*See* Table 7).

[108] **Table 7**

	Baseline	4 weeks	P value[2)]
Obesity Index (%)	131.85 ± 2.81[1)]	127.90 ± 2.63	0.000
BMI (kg/m^2)	27.40 ± 0.58	26.61 ± 0.54	0.000
Weight (kg)	71.28 ± 1.97	69.37 ± 1.88	0.000
Waist (cm)	87.52 ± 2.10	8408 ± 1.82	0.002
Hip (cm)	102.13 ± 1.38	101.34 ± 1.23	0.214
WHR	0.86 ± 0.01	0.83 ± 0.01	0.017

[109] [1)] Mean ± SE

[110] [2)] Statistical significance was evaluated by paired t-test

[111] **2-3. Effect of the KSH28 on the body composition**

[112] The body composition such as total body fat mass, abdominal fat percent, lean body mass, water, protein, mineral was measured with body fat measurer (Biospace Co., Inbody 2.0), of which confidence and validity has been authorized by several literatures (Yim, HJ. And Yoon, JS., *The Korean Nutrition Society*, 28(9), pp893-903, 1995; Likaski HC., *Am. J. Clin. Nutr.*, 46, pp537-556, 1987). The value of muscle mass herein indicates the sum of body and water protein and the value of abdominal fat percentage indicates the value provided with the machinery.

[113] At the result of the experiment, the fat mass($p<0.001$) was significantly reduced by 1.77kg averagely, the percent body fat ($p<0.01$) was reduced by 1.63% after taking the natural food of the present invention for 4 weeks (*See* Table 8). The loss of body weight was derived from the decrease of the fatty tissue, while the decrease of the water, protein, muscle and mineral were not appeared.

[114] Generally, in conventional diet therapy, the water in body is reduced in initial stage and the protein and muscle mass is further reduced by fasting and diet program. the results of the present research showed that only the fat component was reduced without loss of protein or muscle mass, which is confirmed that the ingestion of inventive composition can be more useful and healthy therapy to treat obesity than conventional diet therapy.

[115] **Table 8**

	Baseline	4 weeks	P value[2)]

Fat mass (kg)	23.75 ± 1.12 [1)]	21.98 ± 1.08	0.000
Fat %	33.54 ± 0.96	31.91 ± 1.06	0.004
Abdominal Fat	0.92 ± 0.01	0.91 ± 0.01	0.000
Water (kg)	33.40 ± 1.21	32.41 ± 1.03	0.284
Protein (kg)	11.90 ± 0.34	11.90 ± 0.38	0.982
Muscle (kg)	43.79 ± 1.33	43.48 ± 1.40	0.791
Mineral (kg)	2.63 ± 0.06	2.63 ± 0.07	0.979

[116] [1)] Mean ± SE

[117] [2)] Statistical significance was evaluated by paired t-test

[118] **2-4. Effect of the KSH28 on the blood fat**

[119] To investigate the glucose and lipid in fasting blood glucose, total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and TG(triglyceride) analysis was determined by using cholesterol LDX apparatus (Cholestech Corporation Co., US).

[120] To investigate the liver function, the activity of the serum glutamyl-pyruvate transaminase (GPT) was determined by using Reflotron plus apparatus (Roche Co., Switzerland).

[121] At the result of the experiment, the values of total cholesterol ($p<0.001$), LDL cholesterol and HDL cholesterol ($p<0.001$) were significantly reduced. Especially, the values in 7 persons among 14 persons classified into high-risky group having total cholesterol above 230 were remarkably reduced to the normal range. There have been not observed in the change of VLDL cholesterol (very low density lipoprotein-cholesterol) and triglyceride, however, the blood glucose ($p<0.05$) level was significantly reduced. Also, the change of serum GPT value representing liver function was not observed in particular. The GPT values in 2 persons belonged to abnormal range (>45) group were recovered to normal range of the GPT value due to intake of the natural food of the present invention (*See* Table 9).

[122] **Table 9**

	Baseline	4 weeks	P value[2)]
Total Cholesterol (mg/dL)	217.54 ± 6.67	198.77 ± 7.06	0.000
HDL Cholesterol	54.77 ± 1.64	47.95 ± 1.62	0.000

(mg/dL)			
LDL Cholesterol (mg/dL)	135.21 ± 5.96	122.84 ± 5.68	0.014
VLDL Cholesterol (mg/dL)	25.81 ± 2.00	25.14 ± 1.75	0.714
Triglyceride (mg/dL)	136.89 ± 12.35	127.50 ± 8.71	0.387
Glucose (mg/dL)	121.18 ± 3.99	115.90 ± 3.82	0.040
GPT (U/L)	15.69 ± 1.73	16.95 ± 1.71	0.494

[123] [1)] Mean ± SE

[124] [2)] Statistical significance was evaluated by paired t-test

[125] **2-5. Effect of KSH28 on the Blood pressure and Pulse**

[126] At the result of the experiment, both SBP (systolic blood pressure, $p<0.05$) value and DBP (diastolic blood pressure, $p<0.05$) value were significantly reduced, while the change of the pulse was not observed (*See* Table 10).

[127] **Table 10**

	Baseline	4 weeks	P value[2)]
SBP (mmHg)	125.38 ± 2.56	121.15 ± 2.43	0.017
DBP (mmHg)	80.13 ± 1.89	76.15 ± 1.46	0.016
Pulse (/min)	71.45 ± 1.34	71.97 ± 1.40	0.698

[128] [1)] Mean ± SE

[129] [2)] Statistical significance was evaluated by paired t-test

[130] **2-6. Effect of KSH28 on the ingested amount of a diet**

[131] The comparison result of the ingested amount of the nutrition at the point before and after taking the inventive meal for 4 weeks was shown in Table 11.

[132] There was no significant difference in respect to total calorie since all subjects were allowed to take other foods freely with the natural food of the present invention. Although,

[133] the ingested amount of protein was not changed, the ingested amount of fat and carbohydrate as well as cholesterol was significantly reduced. The ingested amount of dietary fiber was greatly increased because of the effect of the dietary fiber in inventive natural food.

[134] **Table 11**

		Base line	4 week	p-value[2)]
Energy	(kcal)	17243521 ± 81.19	1659.04 ± 50.63 [1)]	0.544
Protein	(g)	6434 ± 454	67.16 ± 1.98	0.576
Fat	(g)	4341 ± 426	31.43 ± 2.05	0.033
Carbohydrate	(g)	255.59 ± 16.89	14420 ± 7.63	0.000
P : C : F		15.4:61.2:234	238:51.1:25.1	
Dietary fiber	(g)	7.27 ± 0.57	3497 ± 0.24	0.000
Cholesterol	(mg)	25480 ± 35.93	157.85 ± 1375	0.031

[135] [1)] Mean ± SE

[136] [2)] Statistical significance was evaluated by paired t-test.

[137] P : C : F : Percentage energy intakes ratio of protein, carbohydrate and fat

[138] Hereinafter, the formulating methods and kinds of excipients will be described, but the present invention is not limited to them. The representative preparation examples were described as follows.

[139] Preparation of powder

[140] Dried powder of Example3 ····· 50mg

[141] Lactose ····· 100mg

[142] Talc ····· 10mg

[143] Powder preparation was prepared by mixing above components and filling sealed package.

[144] Preparation of tablet

[145] Dried powder of Example3 ····· 50mg

[146] Corn Starch ····· 100mg

[147] Lactose ····· 100mg

[148] Magnesium Stearate ····· 2mg

[149] Tablet preparation was prepared by mixing above components and entabletting.

[150] Preparation of capsule

[151] Dried powder of Example3 ····· 50mg

[152] Corn starch ····· 100mg

[153] Lactose ····· 100mg

[154] Magnesium Stearate 2mg

[155] Tablet preparation was prepared by mixing above components and filling gelatin capsule by conventional gelatin preparation method.

[156] Preparation of injection

[157] Dried powder of Example 3 ..... 50mg

[158] Distilled water for injection optimum amount

[159] PH controller optimum amount

[160] Injection preparation was prepared by dissolving active component, controlling pH to about 7.5 and then filling all the components in 2ml ample and sterilizing by conventional injection preparation method.

[161] Preparation of liquid

[162] Dried powder of Example 3 ..... 0.1~80g

[163] Sugar ..... 5~10g

[164] Citric acid ..... 0.05~0.3%

[165] Caramel ..... 0.005~0.02%

[166] Vitamin C ..... 0.1~1%

[167] Distilled water ..... 79~94%

[168] CO_2 gas ..... 0.5~0.82%

[169] Liquid preparation was prepared by dissolving active component, filling all the components and sterilizing by conventional liquid preparation method.

[170] Preparation of health food

[171] Dried powderof Example 3 ..... 1000mg

[172] Vitamin mixture ..... optimum amount

[173] Vitamin A acetate 70mg

[174] Vitamin E 1.0mg

[175] Vitamin B_1 ..... 0.13mg

[176] Vitamin B_2 ..... 0.15mg

[177] Vitamin B_6 ..... 0.5mg

[178] Vitamin B_{12} 0.2mg

[179] Vitamin C 10mg

[180] Biotin 10mg

[181] Amide nicotinic acid 1.7mg

[182] Folic acid 50mg

[183] Calcium pantothenic acid 0.5mg

[184] Mineral mixture ..... optimum amount

[185] Ferrous sulfate 1.75mg
[186] Zinc oxide 0.82mg
[187] Magnesium carbonate 25.3mg
[188] Monopotassium phosphate 15mg
[189] Dicalcium phosphate 55mg
[190] Potassium citrate 90mg
[191] Calcium carbonate 100mg
[192] Magnesium chloride 248mg

[193] The above-mentioned vitamin and mineral mixture may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention.

[194] Preparation of health beverage

[195] Dried powderof Example 3 ..... 1000mg
[196] Citric acid 1000mg
[197] Oligosaccharide 100g
[198] Apricot concentration 2g
[199] Taurine 1g
[200] Distilled water ..... 900 ml

[201] Health beverage preparation was prepared by dissolving active component, mixing, stirred at 85° C for 1 hour, filtered and then filling all the components in 1000 ml ample and sterilizing by conventional health beverage preparation method.

[202] The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

Industrial Applicability

[203] As described in the present invention, the composition comprising the extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis* and *Nelumbo nucifera* has reducing effect on the body weight, blood pressure and cholesterol, therefore, it can be useful as the therapeutics or health food for treating and preventing obesity and adult diseases.

Claims

[1] 1. A pharmaceutical composition comprising the crude drug extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis and Nelumbo nucifera* as an active ingredient for the treatment and prevention of obesity and adult disease.

[2] 2. The pharmaceutical composition wherein ratio of crude drugs in the composition is 30 to 45 % *Coix lachrymajobi*, 30 to 45 % *Castanea crenata*, 5 to 15% *Cervus elaphus*, 2 to 10 % *Schizandra chinensis* and 1 to 6 % *Nelumbo nucifera* based on the total weight of the composition.

[3] 3 The pharmaceutical composition according to claim 1 or 2 wherein said extract further contains Chinese herb selected from the group consisting of *Dioscorea batatas, Platycodon grandiflorum, Liriope platyphylla, Morus alba, Raphanus sativus, Pyrus ussuriensis, Prunus mune, Phyllostachys bambusoides*and*Angelica keiskei.*

[4] 4 A use of crude drug extract as set forth in claim 1 or 3 for the preparation of therapeutic agent for the treatment and prevention of obesity and adult disease in human or mammal.

[5] 5. A health care food comprising crude drug extract of *Coix lachrymajobi, Castanea crenata, Cervus elaphus, Schizandra chinensis and Nelumbo nucifera* as an active ingredient, together with a sitologically acceptable additive for prevention and improvement of obesity and adult disease.

[6] 6. The health care food according to claim 5 wherein the composition is consisting of 30 to 45% *Coix lachrymajobi*, 30 to 45% *Castanea crenata*, 5 to 15% *Cervus elaphus*, 2 to 10 % *Schizandra chinensis* and 1 to 6 % *Nehumbo nucifera.*

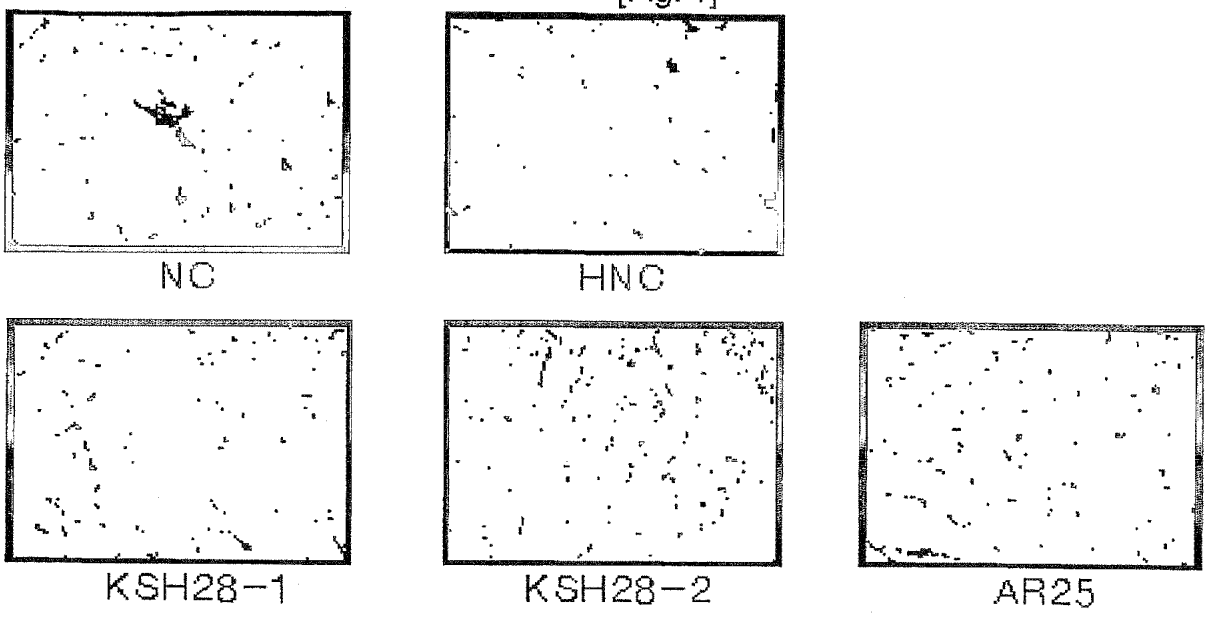
[7] 7. The health care food according to claim 5 wherein said extract further contains Chinese herb selected from the group consisting of *Dioscorea batatas, Platycodon grandiflorum, Liriope platyphylla, Morus alba, Raphanus sativus, Pyrus ussuriensis, Prunus mune, Phyllostachys bambusoides* and *Angelica keiskei.*

[8] 8. The health care food according to any of claims 5 to 7 wherein said health food is provided as powder, granule, tablet, chewing tablet, capsule beverage or natural meal type.

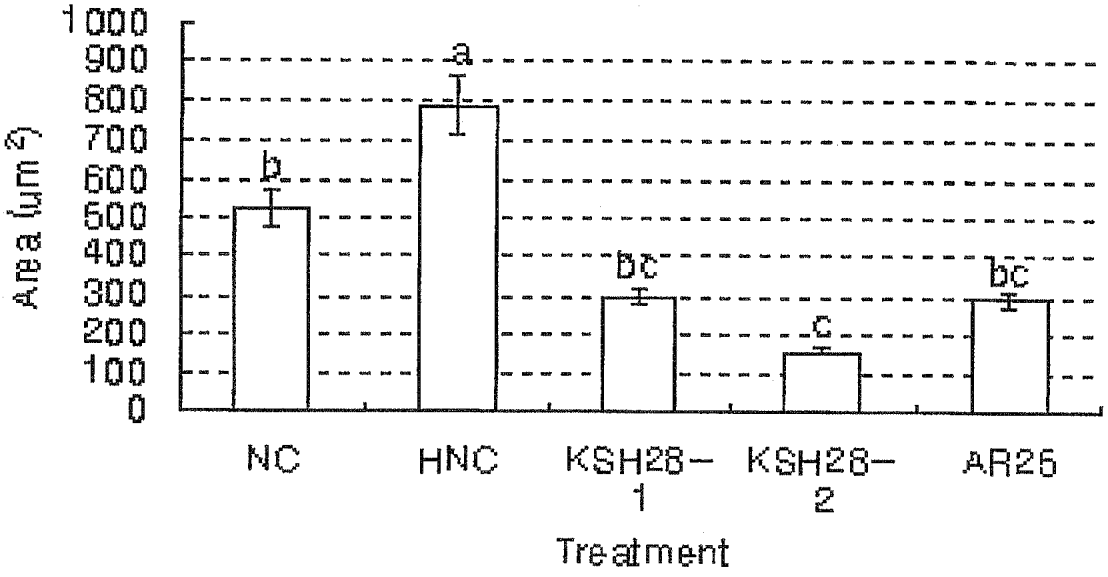
[9] 9. The health care food according to claim 8 said natural meal is consisting

of KSH28, provided as brown rice, wheat, soybean, pea, oyster mushroom, shiitake fungus, dried laver, dried kelp, carrot, codonopsis root, lotus root, glucomannan, Vt. B_1, Vt. B_2, Vt. B_6, Vt. D_3, Vt. C, inositol, ZnO, L-organic calcium and stevioside.

[Fig. 1]



[Fig. 2]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/000609

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 35/78, A23L 1/29

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
PubMed on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KR 2001-0088728 A (HELPER LAB CO., LTD.), 28 September 2001 See entire document	1-9
Y	KR 2002-0077581 A (BAEYOUNG SCHOOL FOUNDATION), 12 October 2002 See entire document	1-9
Y	JP 08-198769 A (POLA CHEM. IND. INC.), 06 August 1996 See entire document	1-9
Y	KR 1998-0067315 A (KIM, DR), 15 October 1998 See entire document	1-9
Y	JP 2002-275078 A (KANEBO LTD.), 25 September 2002 See abstract and claims	1-9
Y	KR 2002-0020305 A (PARK, JS), 15 March 2002 See abstract and claims	1-9
Y	KR 0348818 B1 (CHULLANAM-DO), 09 September 2002 See abstract and claims	1-9

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 MAY 2004 (27.05.2004)	27 MAY 2004 (27.05.2004)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/000609

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN 1062449 A (WANG, D), 08 July 1992 See abstract	1-9
Y	KR 2003-0005086 A (EROMLIFE CO., LTD.), 15 January 2003 See claims	1-9
A	KR 2002-0095513 A (KOREA INSTITUTE OF ORIENTAL MEDICINE), 27 December 2002 See abstract and claims	3, 4, 7-9
A	JP 2002-356434 A (NICCA CHEMICAL CO., LTD.), 13 December 2002 See abstract	3, 4, 7-9
A	JP 61-112024 A (HORIUCHI :KK et al.), 30 May 1986 See abstract	3, 4, 7-9
A	JP 08-198767 A2 (POLA CHEM. IND. INC.), 06 August 1996 See abstract	3, 4, 7-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/000609

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-4 concern a pharmaceutical composition for the treatment and prevention of obesity and adult disease, and claims 5-9 concern a health care food for the prevention and improvement of obesity and adult disease.

Although claims 1-4 and 5-9 are relevant to the composition comprising the same active ingredient, there is no technical relationship among a pharmaceutical composition and health care food.

Hence, the application contains the following separate groups of inventions not so linked as to form a single general inventive concept (PCT Rule 13.1) :

i) Claims 1-4
ii) Claims 5-9

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2004/000609

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 2001-0088728 A	28/09/2001	NONE	
KR 2002-0077581 A	12/10/2002	NONE	
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JP 08-198767 A2	06/08/1996	NONE	